STRUCTURAL BIOLOGY OF MEMBRANE PROTEINS

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P.T.

National Institute of General Medical Sciences
National Institute of Arthritis and Musculoskeletal and Skin Diseases
National Institute of Diabetes and Digestive and Kidney Diseases
National Institute of Environmental Health Sciences
National Institute of Neurological Disorders and Stroke

PURPOSE

The purpose of this program announcement (PA) is to encourage basic research on the structures of membrane proteins at (or near) atomic resolution. Considerable research is on-going in the area of membrane protein structure and function, particularly with respect to sequences, topology, and the effects of mutations; however, much of this work is somewhat speculative in that the interpretations depend upon the very limited number of structures that have actually been solved by direct biophysical measurements. Despite several recent landmark solutions of membrane protein structures, there remains a significant gap between the understanding of membrane proteins and that of their soluble counterparts. This gap will likely increase as the facility with which soluble protein structures can be solved continues to increase. Therefore, it is clear that a special effort is needed to promote studies of membrane protein structures. An increase in the number of known membrane protein structures will contribute to an enhanced understanding of many basic phenomena underlying cellular functions essential to human health.

HEALTHY PEOPLE 2000

The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2000," a PHS led national activity for setting priority areas. This Program Announcement (PA), Title of PA, is related to one or more of the priority areas. Potential applicants may obtain a copy of "Healthy People 2000" at http://www.crisny.org/health/us/health7.html.

ELIGIBILITY REQUIREMENTS

Applications may be submitted by foreign and domestic, for-profit and non-profit organizations, public and private, such as universities, colleges, hospitals, laboratories, units of State and local governments, and eligible agencies of the Federal government. Racial/ethnic minority individuals, women, and persons with disabilities are encouraged to apply as principal investigators. Foreign institutions are not eligible for the SBIR (R43, R44), STTR(R41, R42), or program project (P01) grant mechanisms.

MECHANISM OF SUPPORT

Support of this program will be through the individual research project grant (R01), program project grant (P01). Applicants may also apply for the Small Business Innovation Research (R43, R44) and Small Business Technology Transfer (R41, R42) award mechanisms. Details of STTR and SBIR mechanisms (i.e., application procedures, review procedures) are provided in the Omnibus Solicitations of the NIH, CDC, and FDA for Small Business Innovation Research Grant Applications (SBIR 98-2) and the Omnibus Solicitation of the National Institutes of Health for Small Business Technology Transfer Grant Applications (PHS 98-3). These documents are available on the NIH Website: http://www.nih.gov/grants/funding/sbir.htm. Copies may also be obtained by calling the SBIR/STTR Solicitation Office: 301-206-9385.

Investigators holding active R01, P01, or MERIT (R37) grants to study membrane associated processes, but who are not currently supported for work on high resolution structural studies of the relevant membrane associated proteins, may wish to consider applying for competing supplemental awards, if they would have at least one year remaining in the project period at the time of supplement funding.

All potential applicants are strongly urged to contact the program staff listed under INQUIRIES for guidance in the areas appropriate for this program, especially if submission of a program project or supplemental grant application is being considered

RESEARCH OBJECTIVES

Membrane proteins play a crucial role in many cellular and physiological processes. They are essential mediators of material and information transfer between cells and their environment, between compartments within cells, and between compartments comprising the organ systems.

Functionally normal membrane proteins are vital to health and specific defects are associated with many known disease states. Membrane proteins are the targets of a large number of pharmacologically and toxicologically active substances and are responsible, in part, for their uptake, metabolism, and clearance.

Despite the importance of membrane associated proteins, the knowledge of their high resolution structures and mechanisms of action has lagged far behind the knowledge of these properties of proteins in general. This has resulted from the difficulty of obtaining x-ray diffraction quality crystals for the membrane-embedded domains of these proteins and the difficulty of applying well developed solution NMR methods to the study of most membrane proteins. These difficulties have led to a reluctance of many investigators to pursue high resolution structural studies of membrane proteins. However, in the recent past, advances in methods for crystallization and analysis of proteins by x-ray and electron diffraction methods, and improvements in NMR methods, particularly solid-state NMR, have led to new opportunities. Further, the solution of crystal structures, once suitable crystals are obtained has, in many cases, become sufficiently routine, that crystallization itself is often a major undertaking worthy of financial support. The objective of this program announcement is two-fold:

1) To encourage investigators with interests in membrane associated systems to pursue high resolution structural studies making use of these recently developed technologies; and

2) To encourage additional research to further develop methods for studying the structure of membrane proteins at atomic resolution. Areas identified as needing specific attention include:

o Improved methods for over-expression of native and modified membrane proteins,

o Improved methods for isolation, purification, and stabilization of membrane proteins, including the development of new detergents and non-detergent solubilization agents,

o Basic research on the physical chemistry of membrane protein crystallization and the development of new methods for crystallization and crystal manipulation that could facilitate data collection,

o Further development of methods for electron diffraction, particularly for the production of suitable 2D-crystals,

o Further development of NMR methods for examining membrane proteins in their native lipid environments.

The techniques of x-ray or electron diffraction and of NMR spectroscopy have been emphasized in this announcement, since it is felt that they show the most promise for producing complete high resolution information for the largest number of proteins. However, funds are also available for research using other methods that can provide atomic resolution information in selected cases. Methods that can elucidate the organization of lipid and detergent molecules within protein crystalline arrays (e.g., neutron diffraction) are also of interest.

It is expected that many of the projects will be collaborative efforts between biochemists and molecular biologists with expertise in the isolation and characterization of membrane-bound proteins and biophysicists with expertise in x-ray crystallography, NMR, and other structural methods. A major aim of this program announcement is to stimulate such collaborations.

Membrane protein systems of particular interest to the National Institute of General Medical Sciences (NIGMS) include: energy transducing membranes of mitochondria, chloroplasts, and bacterial cell membranes involved in electron transport and ATP synthesis; transporters of ions, substrates, and macromolecules between intracellular compartments and between the cell and its environment; enzymes in the synthesis and metabolism of lipids, membrane-associated and secreted proteins, and glycoconjugates; cytoskeletal proteins, including those required for intracellular vesicle transport, cell motility, and cell division; regulators of cell-cell communication, differentiation, and growth; receptors relevant to cell cycle regulation, mechanisms of anesthetic action, and trauma and burn physiology; transporters and enzymes responsible for the uptake, metabolism, and clearance of drugs, or in other ways affecting the bioavailability, pharmacokinetics, or action of drugs; targets of drug action and toxicity, including targets of naturally occurring toxins and venoms; enzymes involved in the biosynthesis of natural products.

Membrane protein systems of interest to the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) have specific relevance to one of the following programmatic areas: muscle function and disease; bone and cartilage function and disease; skin function and disease. Examples of NIAMS interests are: structural aspects of membrane proteins in muscle disease, excitation, relaxation, force transduction, cellular homeostasis and metabolism, regulators of cell-cell communication and attachment (e.g. costameres, myotendinous and neuromuscular junctions), ion channels, receptors, transporters and enzymes that effect muscle function and hypertrophy or atrophy; and structural aspects of membrane proteins in skin as they are involved in the establishment of the stratum corneum barrier, epidermal cell-cell attachment and

communication, transmembrane signaling and transport, and cell movement, including genetic and acquired diseases of skin in which the membrane protein is defective or targeted (which may encompass both benign and malignant hyperproliferative diseases).

Membrane protein systems of particular interest to the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) should have specific relevance to one of the following programmatic areas: diseases of transport such as cystic fibrosis and peroxisomal biogenesis disorders; carbohydrate metabolism and its hormonal control; diabetes mellitus; hormone receptors and signal transduction; endocrine disorders; normal and abnormal processes of lipid, protein, amino acid, urea, pyrimidine, metal ion and steroid metabolism; genetic metabolic disorders. Proteins should be of mammalian origin. Studies on proteins of prokaryotic or lower eukaryotic origin should be proposed as models for mammalian systems. An example of this is the ABC transporter superfamily or traffic ATPases in bacteria and yeast that serve as models for the cystic fibrosis transmembrane regulator (CFTR).

Membrane protein systems of particular interest to the National Institute of Environmental Health Sciences (NIEHS) include those proteins/enzymes involved in the response of cells to environmental toxicants. These proteins/enzymes may include the components of the stress signaling pathway, ion channels involved in transport of xenobiotics, i.e., membrane transporters as PgP and MDR, MRP2 , transporters and enzymes responsible for the uptake metabolism and clearance of environmental toxicants, targets of toxicant action including the Ah receptor nonclassical receptors for endocrine disrupting agents, and membrane bound heat shock proteins.

Membrane protein systems of interest to the National Institute of Neurological Disorders and Stroke (NINDS) include receptors, ion channels, structural proteins and other proteins involved in the normal function and pathology of nerve cells in the central and peripheral nervous system. These include ion-selective channels such as sodium, potassium, and calcium channels; ligand-gated ion channels such as cholinergic, glutamatergic, gabaergic and glycinergic receptors; compartmental and cytoskeletal elements involved in protein trafficking and assembly, neurite growth, cell adhesion, cell migration, synaptic structure, and vesicular release; G protein-linked receptors; trophic factor receptors; and transporters and pumps for ions, transmitters or macromolecules. Studies of conformational changes involved in normal function, in the action of drugs, and in dysfunction of mutated proteins associated with neurodevelopmental or neurodegenerative disorders are of particular interest. Protein-protein interactions important for higher order structural assemblies and for pathological associations characteristic of neurofilament, amyloid, Lewy body and prion diseases are also of interest.

The above listings are not meant to be exclusive. Structural information obtained for any membrane protein will contribute to understanding the general principles that underlie all membrane protein structure and function. Research on the non-membrane embedded proteins associated with many of the cellular functions listed above is also supported by the participating Institutes; however, this program announcement is intended to emphasize the need for additional research on structural aspects of the membrane-embedded proteins involved in these processes.

APPLICATION PROCEDURES

Applications for R01 and P01 grants are to be submitted on the grant application form PHS 398 (rev. 5/95) and will be accepted at the standard application deadlines as indicated in the application kit. Application kits are available at most institutional offices of sponsored research and may be obtained from the Division of Extramural Outreach and Information Resources, 6701 Rockledge Drive, MSC 7910, Bethesda, MD 20892-7910, telephone 301-435-0714, Email grantsinfo@nih.gov.

Applications for the SBIR and STTR mechanisms are to be submitted on the forms available in the Omnibus solicitations and will be accepted on the SBIR and STTR application receipt dates.

Applicants planning to submit an investigator-initiated new (type 1), competing continuation (type 2), competing supplement, or any amended/revised version of the preceding grant application types requesting $500,000 or more in direct costs for any year are advised that he or she must contact the Institute or Center (IC) program staff before submitting the application, i.e, as plans for the study are being developed. Furthermore, the application must obtain agreement from the IC staff that the IC will accept the application for consideration for award. Finally, the applicant must identify, in a cover letter sent with the application, the staff member and Institute or Center who agreed to accept assignment of the application. This policy requires an applicant to obtain agreement for acceptance of both any such application and any such subsequent amendment. Refer to the NIH Guide for Grants and Contracts, March 20, 1998 at http://www.nih.gov/grants/guide/notice-files/not98-030.html

The title and number of the program announcement must be typed in Section 2a on the face page of the application (i.e., "Structural Biology of Membrane Proteins," PA-99-004).

Submit a signed, typewritten original of the application, including the Checklist, and five signed photocopies in one package to:

CENTER FOR SCIENTIFIC REVIEW
NATIONAL INSTITUTES OF HEALTH
6701 ROCKLEDGE DRIVE, ROOM 1040, MSC 7710
BETHESDA, MD 20892-7710
BETHESDA, MD 20817-7710 (for express/courier service)

REVIEW CONSIDERATIONS

Applications will be assigned on the basis of established PHS referral guidelines. Applications will be evaluated for scientific and technical merit by appropriate scientific review groups convened in accordance with the standard NIH peer review procedures. As part of the initial merit review, all applications will receive a written critique and undergo a process in which only those applications deemed to have the highest scientific merit, generally the top half of applications under review, will be discussed, assigned a priority score, and receive a second level review by the appropriate national advisory council or board.

Review criteria for STTR (R41 and R42) and SBIR (R43 and R44) applications can be found in the omnibus solicitation references above under Mechanism of Support.

Review Criteria for R01s and P01s:

The goals of NIH-supported research are to advance our understanding of biological systems, improve the control of disease, and enhance health. In the written comments, reviewers will be asked to discuss the following aspects of the application in order to judge the likelihood that the proposed research will have a substantial impact on the pursuit of these goals. Each of these criteria will be addressed and considered in assigning the overall score, weighting them as appropriate for each application. Note that the application does not need to be strong in all categories to be judged likely to have major scientific impact and thus deserve a high priority score. For example, an investigator may propose to carry out important work that by its nature is not innovative but is essential to move a field forward.

(1) Significance: Does this study address an important problem? If the aims of the application are achieved, how will scientific knowledge be advanced? What will be the effect of these studies on the concepts or methods that drive this field?

(2) Approach: Are the conceptual framework, design, methods, and analyses adequately developed, well-integrated, and appropriate to the aims of the project? Does the applicant acknowledge potential problem areas and consider alternative tactics?

(3) Innovation: Does the project employ novel concepts, approaches or methods? Are the aims original and innovative? Does the project challenge existing paradigms or develop new methodologies or technologies?

(4) Investigator: Is the investigator appropriately trained and well suited to carry out this work? Is the work proposed appropriate to the experience level of the principal investigator and other researchers (if any)?

(5) Environment: Does the scientific environment in which the work will be done contribute to the probability of success? Do the proposed experiments take advantage of unique features of the scientific environment or employ useful collaborative arrangements? Is there evidence of institutional support?

In addition to the above criteria, in accordance with NIH policy, all applications will also be reviewed with respect to the following:

o The adequacy of plans to include both genders, minorities and their subgroups, and children as appropriate for the scientific goals of the research. Plans for the recruitment and retention of subjects will also be evaluated.

o The reasonableness of the proposed budget and duration in relation to the proposed research.

o The adequacy of the proposed protection for humans, animals or the environment, to the extent they may be adversely affected by the project proposed in the application.

AWARD CRITERIA

Applications will compete for available funds with all other approved applications. The following will be considered in making funding decisions:

o quality of the proposed project as determined by peer review;
o availability of funds;

o program priority of research in the area of the program announcement and other areas of Institute interest.

INQUIRIES

Inquiries are encouraged. The opportunity to clarify any issues or questions from potential applicants is welcome.

Direct inquiries regarding programmatic issues to:

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AUTHORITY AND REGULATIONS

This program is described in the Catalog of Federal Domestic Assistance Nos. 93.113, 93.821, 93.846, 93.847, 93.854, and. 93.859. Awards are made under authorization of the Public Health Service Act, Title IV, Part A (Public Law 78-410, as amended by Public Law 99-158, 42 USC 285c-8 and 285k) and administered under PHS grants policies and Federal Regulations 42 CFR 52 and 45 CFR Part 74. This program is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review.

The PHS strongly encourages all grant and contract recipients to provide a smoke-free workplace and promote the non-use of all tobacco products. In addition, Public Law 103-227, the Pro-Children Act of 1994, prohibits smoking in certain facilities (or in some cases, any portion of a facility) in which regular or routine education, library, day care, health care or early childhood development services are provided to children. This is consistent with the PHS mission to protect and advance the physical and mental health of the American people.

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